REMARKS

I. Prosecution Procedure and Examination

The Restriction Requirement begins by stating that claim 1 "does not allow for proper restriction" (Requirement, opening sentence). Surely, therefore, claim 1 should not be subject to restriction? After all, there is no statutory, judicial or regulatory requirement that a patent application *must be* subject to restriction. Moreover, as claim 1 admittedly does not allow for "proper" restriction, but a restriction is applied, it can only be concluded that the proposed restriction must be "improper".

The Requirement then continues to present what appears to be an examination of the claims under 35 U.S.C. § 112, second paragraph. It is first alleged that claim 1 is unclear in the recitation of "a first antibody" when the claim does not require a "second antibody". First, the claim in fact requires "at least a first antibody", which means that there may, or may not, be a second antibody. Second, the invention is defined by the pending claims, not claim 1 in isolation, and claim 12 positively recites "at least a first and second antibody", thus further limiting claim 1.

It is next alleged that the phrase "second agent" is not clear because there is no "first agent" recited. Claim 1 actually recites a "second anti-cancer agent", which is perfectly clear when read in light of the specification. The present application explains that the primary "anti-cancer agent" of the invention is the naked antibody or fragment that binds to an aminophospholipid. Therefore, when combined with another agent for treating cancer, the combined agent may be termed either a "first" or "second" anti-cancer agent. The specification states:

> "In still further embodiments, the animals or patients to be treated by the present invention are further subjected to surgery or radiotherapy, or are provided with a therapeutically effective amount of at least a first anti-cancer agent. The "at least a first anti-cancer agent" in this context means "at least a first anti-cancer agent in addition to the naked anti-aminophospholipid antibody" (preferably anti-phosphatidylserine or anti-phosphatidylethanolamine). The "at least a first anti-cancer agent" may thus be considered to be "at least a second anti-cancer agent", where the naked anti-aminophospholipid antibody is a first anti-cancer agent. However, this is purely a matter of semantics, and the practical meaning will be clear to those of ordinary skill in the art.
>
> Specification at page 32, lines 1-9,

Claims 34 and 37 would also be clear to one of ordinary skill in the art in light of the specification.

The Requirement further hints that there could be some lack of clarity in the term "anti-cancer agent", as the agent "could be among a plethora of compounds, such as antibodies, DNA or chemical compounds" (Requirement, opening paragraph). In contrast, "breadth of a claim is not to be equated with indefiniteness". *In re Miller*, 169 USPQ 597 (C.C.P.A. 1971). As the Requirement clearly understands the terminology, it cannot be held to be unclear.

The Requirement continues to criticize the term "anti-cancer agent" as being "functional", apparently taking the position that only "restricted terms based on structure" are proper (Requirement, opening paragraph). Such a position is unsupported by statute or case law. "The proper test of definiteness is whether, in the light of the teachings of the prior art and of the particular application disclosure, the claims set out and circumscribe, for one possessing an ordinary level of skill in the pertinent art, a particular area with a reasonable degree of particularity." *In re Moore*, 169 USPQ 236 (C.C.P.A. 1971). This is clearly achieved by the present specification.

It is next alleged that claim 38 is improper "because the language of the claim 'in combination' can encompass a method, a product, a kit, a composition, a method of combining, *etc.*", so that it is allegedly not clear to what type of statutory invention claim 38 belongs. Applicants respectfully point out that as claim 38 has no method "steps", it cannot be a method. This format of claim is also quite typical in the biotechnology arts, and Applicants respectfully refer to U.S. Patent No. 5,863,538, where the opening claim is in this format.

II. Restriction Requirement

The Requirement alleges that claims 1-38 have been presented in "improper format", apparently because they recite various embodiments that the Office does not consider to be proper species (Requirement bridging pages 2 and 3). The Requirement then summarily states that to "allow Applicant an opportunity to correct these errors", Applicant is invited to "amend the claims to address the various issues raised above" (Requirement at page 3).

The "issues" from page 2 have been fully addressed and shown to be improper (see **Section I**). The refusal to include claim 38 in the restriction analysis is particularly instructive as this claim encompasses not only Groups I and II, but also Groups III and IV.

The allegation that the claims are improper because phosphatidylethanolamine and phosphatidylserine are not proper species of aminophospholipid (Requirement bridging pages 2 and 3) requires no correction because phosphatidylethanolamine and phosphatidylserine are indeed species of aminophospholipid.

The Requirement alleges that claims 1-38 are directed to four distinct inventions under 35 U.S.C. § 121, apparently set forth as:

Group I: Claims 1 and 31, in part, said to be drawn to a kit comprising an antibody that binds to phosphatidylethanolamine and a detectably-labeled antibody, classified in class 530, subclass 388.9;

Group II: Claims 1 and 31, in part, said to be drawn to a kit comprising an antibody that binds to phosphatidylserine and a detectably-labeled antibody, classified in class 530, subclass 388.9;

Group III: Claims 1, 34, and 37, in part, said to be drawn to a kit comprising an antibody that binds to phosphatidylethanolamine and an anti-cancer antibody, classified in class 530, subclass 388.9; and

Group IV: Claims 1, 34, and 37, in part, said to be drawn to a kit comprising an antibody that binds to phosphatidylserine and an anti-cancer antibody, classified in class 530, subclass 388.9.

The fact that the recited anti-cancer "agent" has been interpreted to be an anti-cancer "antibody" (Requirement at page 3) is not only at odds with the plain meaning of this term and the present specification, but is also in marked contrast to page 2 of the Requirement, which states that the anti-cancer agent "could be among a plethora of compounds, such as antibodies, DNA or chemical compounds".

The inventions of Groups I-IV are alleged to represent "separate and distinct products which [are] structurally and functionally distinct" (Requirement at page 4). It is further alleged that the inventions have "different classifications" (Requirement at page 4).

III. Summary of Traversal

Aside from representing an examination for compliance with 35 U.S.C. § 112, second and fourth paragraphs, the Restriction Requirement contains procedural errors of such magnitude that Applicants are compelled to traverse. The most significant errors in the attempted Restriction are that the Office has imposed arbitrary meanings that are entirely at odds with the claim language and has totally ignored recited claim elements. Other notable errors include the fact that claim 1 is included within each group; and that the claims of each Group fall within exactly the same class and subclass. The Requirement has therefore ignored the long established practice regarding linking claims that cover species within a generic invention. The Requirement

further fails to provide adequate reasoning to show that the inventions are "distinct" and, even if the inventions were distinct, does not apply proper restriction procedure. The Requirement is also significantly at odds with the Restriction Requirements issued in related co-pending applications, one of which contains kit claims of a similar format to the present claims.

Applicants therefore traverse the Restriction Requirement on the basis that it is inconsistent with many grounds of long-established U.S. Restriction practice.

IV. Detailed Traversal

The procedures of the Office assigning arbitrary meanings to claims that are at odds with the claims themselves and ignoring recited claim elements are totally improper, and have no statutory, judicial or regulatory bases. The application of such procedures is a significant flaw in the present Restriction.

For example, there is nothing in claims 1, 34, 37 or 38 to support an interpretation of the claimed antibody as binding to only phosphatidylethanolamine (Group I) or only phosphatidylserine (Group II). Neither is there any justification for selecting only one of the detectably-labeled antibody or second anti-cancer agent, recited in the alternative in claim 1 and in combination in claim 38.

Therefore, claims 1 and 38 are clearly linking claims that properly join the various embodiments of the overall invention. In addition to the foregoing claims being generic to all aspects of the invention, most of the other claims, including claims 34 and 37, are sub-generic to a variety of species. Therefore, rather than being distinct groups, the pending claims reflect species within a proper generic invention, as exemplified by claims 1 and 38.

Scientific reasoning in the Requirement is also at odds with the present specification. For instance, without citing any supporting evidence, the Requirement appears to take the position

that antibodies to phosphatidylethanolamine must be distinct from antibodies to phosphatidylserine (Requirement at page 3 and page 4). In contrast, the present specification explains that cross-reactive anti-aminophospholipid antibodies, which bind to both phosphatidylethanolamine and phosphatidylserine (PS), are suitable for use the invention. The assessment of Group II as requiring antibodies "specific for PS" is particularly in error (Requirement at page 4).

It is thus clear that the claimed invention as a whole is a generic invention that properly links various species. Indeed, the Office has not provided reasoning adequate to show that the inventions of Groups I-IV are properly restrictable or distinct.

MPEP 806.05(c) states that a requirement for restriction must be supported by "both two-way distinctness and reasons for insisting on restriction", such as separate classification, status or field of search, separate particulars of patentability or combinations with distinct utility. MPEP 806.05(c) at page 800-34, column 1. The present Requirement has not provided adequate evidence of distinctness and has certainly not provided any reason for insisting on restriction.

Even presuming that the Office rejects the species analysis set forth above, and maintains that Groups I-VI are "distinct inventions", the distinct inventions must still be maintained in the same case with proper linking claims. MPEP 809 clearly states that, even with distinct inventions, "the linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn." Any claims to non-elected inventions, even if previously canceled, must then be reinstated in the case. MPEP 809 at page 800-39, column 2. As all pending claims in the present application are intimately linked by a variety of generic and sub-generic linking claims, each of claims 1-48 must be maintained in the case even if they are held to be drawn to distinct inventions.

Further compelling evidence for the unified nature of the present claims is that all four allegedly distinct inventions are in fact classified in exactly the same class and subclass. This contradicts the Requirement at page 4, which alleges that the inventions have received "different classifications". Searching only in one class and subclass shows that there would be no undue burden on the Examiner should all claims be examined together. In addition to contravening MPEP 806.05(c), which requires a "separate classification", the Requirement therefore falls foul of MPEP 803, which requires a "serious burden" on the examiner should restriction not be made. "If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." MPEP 803 at page 800-3, column 2.

Important evidence in support of Applicants' position is the extensive unity of claims found in related co-pending applications. Application Serial No. 09/351,149 ("the '149 application"; Attorney Docket No. 4001.002383), already disclosed to the Office, contains a single, unified set of claims drawn to kits comprising aminophospholipid-targeted therapeutic conjugates in combination with either "a detectably-labeled aminophospholipid targeting agent or at least a second anti-cancer agent" (**Exhibit A**). Although the claims in the '149 application first recite an anti-aminophospholipid therapeutic conjugate, rather than the naked antibody of the present invention, the format of the '149 application claims is consistent with that of the present application. The finding of unity in the '149 application is thus compelling.

Applicants further invite the Office to consider the unified claims in Application Serial No. 09/351,457 ("the '457 application"; Attorney Docket No. 4001.002300), already disclosed to the Office. The claims in the '457 application, drawn to various *in vivo* methods of using

aminophospholipid-targeted therapeutic constructs to treat cancer, were also found to constitute a single invention (**Exhibit B**).

The MPEP clearly states that there should be uniform application of the patentability standards. It is specifically stated, "the standards of patentability applied in the examination of claims must be the same throughout the office" (MPEP at page 700-8, column 1). This is highly pertinent to the present kit claims, particularly given the unity of invention assigned to kits of the same claim format but comprising conjugates instead of naked antibodies (**Exhibit A**).

Accordingly, Applicants respectfully traverse the Restriction Requirement on procedural grounds and request that it be withdrawn. Applicants intend to Petition should the Requirement be maintained.

V. Provisional Election and Status of the Claims

Despite Applicants traversal and intent to petition, Applicants undertake every effort to make a provisional election. Applicants provisionally elect a kit comprising an antibody that binds to phosphatidylserine and an anti-cancer agent. Due the numerous errors in the Restriction, this election does not match any group set forth by the Office. Claims 1-38 therefore remain pending in the case.

VI. Conclusion

Other than the enclosed extension fee, no fees should be due in connection with the present paper. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary, the Examiner is respectfully requested to telephone Applicant's representative to discuss deduction from Applicants' representatives' Deposit Account No. 50-0786/4001.002282.

In conclusion, Applicants submit that the present claims define a unified invention and respectfully request that the Restriction Requirement be withdrawn. Should Examiner Helms

have any questions or comments, a telephone call to the undersigned Applicant's representative is earnestly solicited.

Respectfully submitted,

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Date: November 10, 2000

EXHIBIT A
UNIFIED CLAIMS IN SERIAL NO. 09/351,149 (4001.002383)

1. A kit comprising, in a pharmaceutically acceptable form, biologically effective amounts of at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent; and:

(a) a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; or

(b) at least a second anti-cancer agent.

2. The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises a targeting agent that binds to phosphatidylethanolamine.

3. The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises a targeting agent that binds to phosphatidylserine.

4. The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises at least a first anti-aminophospholipid antibody or antigen-binding fragment thereof.

5. The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first IgG or IgM anti-aminophospholipid antibody.

6. The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first scFv, Fv, Fab', Fab or $F(ab')_2$ antigen-binding fragment of an anti-aminophospholipid antibody.

7. The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first recombinant anti-aminophospholipid antibody, or antigen-binding fragment thereof.

8. The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at. least a first human, humanized or part-human chimeric anti-aminophospholipid antibody, or antigen-binding fragment thereof.

9. The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first monoclonal anti-aminophospholipid antibody, or antigen-binding fragment thereof.

10. The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises at least a first aminophospholipid binding protein or an aminophospholipid-binding fragment thereof.

11. The kit of claim 10, wherein said targeting agent-therapeutic agent construct comprises at least a first phosphatidylserine binding protein or a phosphatidylserine-binding fragment thereof.

12. The kit of claim 10, wherein said targeting agent-therapeutic agent construct comprises at least a first phosphatidylethanolamine binding protein or a phosphatidylethanolamine-binding fragment thereof.

13. The kit of claim 10, wherein said targeting agent-therapeutic agent construct comprises at least a first Annexin V or kininogen or an aminophospholipid-binding fragment thereof.

14. The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises at least a first anticellular or cytotoxic agent.

15. The kit of claim 14, wherein said targeting agent-therapeutic agent construct comprises at least a first gelonin, ricin A chain or deglycosylated ricin A chain.

16. The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises at least a first coagulant.

17. The kit of claim 16, wherein said targeting agent-therapeutic agent construct comprises at least a first Tissue Factor, dimeric Tissue Factor, trimeric Tissue Factor, polymeric Tissue Factor, mutant Tissue Factor, truncated Tissue Factor or a Tissue Factor derivative.

18. The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises an anti-phosphatidylserine antibody, or antigen binding fragment thereof, that is directly or indirectly attached to truncated Tissue Factor.

19. The kit of claim 1, wherein said kit comprises at least a first pharmaceutically acceptable formulation suitable for intravenous administration.

20. The kit of claim 1, wherein said kit comprises, in distinct pharmaceutical compositions, said at least a first targeting agent-therapeutic agent construct in combination with said targeting agent-detectable agent construct.

21. The kit of claim 20, wherein said targeting agent-detectable agent construct comprises the X-ray detectable compound bismuth (III), gold (III), lanthanum (III) or lead (II).

22. The kit of claim 20, wherein said targeting agent-detectable agent construct comprises the detectable radioactive ion copper^{67}, gallium^{67}, gallium^{68}, indium^{111}, indium^{113}, iodine^{123}, iodine^{125}, iodine^{131}, mercury^{197}, mercury^{203}, rhenium^{186}, rhenium^{188}, rubidium^{97}, rubidium^{103}, technetium^{99m} or yttrium^{90}.

23. The kit of claim 20, wherein said targeting agent-detectable agent construct comprises the detectable nuclear magnetic spin-resonance isotope cobalt (II), copper (II), chromium (III), dysprosium (III), erbium (III), gadolinium (III), holmium (III), iron (II), iron (III), manganese (II), neodymium (III), nickel (II), samarium (III), terbium (III), vanadium (II) or ytterbium (III).

24. The kit of claim 1, wherein said kit comprises said at least a first targeting agent-therapeutic agent construct in combination with said at least a second anti-cancer agent.

25. The kit of claim 24, wherein said at least a first targeting agent-therapeutic agent construct and said at least a second anti-cancer agent are comprised within a single pharmaceutical composition.

26. The kit of claim 24, wherein said at least a first targeting agent-therapeutic agent construct and said at least a second anti-cancer agent are comprised within distinct pharmaceutical compositions.

27. The kit of claim 24, wherein said at least a second anti-cancer agent is a chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent or apoptosis-inducing agent.

28. The kit of claim 24, wherein said at least a second anti-cancer agent is an antibody-therapeutic agent construct comprising a second targeting antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor stroma or tumor vasculature; wherein said targeting antibody or fragment thereof is operatively linked to a therapeutic agent.

29. The kit of claim 28, wherein said second targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of intratumoral blood vessels of a vascularized tumor.

30. The kit of claim 29, wherein said second targeting antibody, or antigen-binding fragment thereof, binds to a component of intratumoral vasculature selected from the group consisting of an aminophospholipid, endoglin, a TGFβ receptor, E-selectin, P-selectin, VCAM-1, ICAM-1, PSMA, a VEGF/VPF receptor, an FGF receptor, a TIE, $\alpha_v\beta_3$ integrin, pleiotropin, endosialin, an MHC Class II protein, VEGF/VPF, FGF, TGFβ, a ligand that binds to a TIE, a tumor-associated fibronectin isoform, scatter factor/hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF and TIMP.

31. The kit of claim 28, wherein said second targeting antibody, or antigen-binding fragment thereof, is operatively linked to gelonin, deglycosylated ricin A chain, Tissue Factor, truncated Tissue Factor or to an antibody, or antigen-binding fragment thereof, that binds to Tissue Factor or truncated Tissue Factor.

32. The kit of claim 1, wherein said kit comprises biologically effective amounts of:

(a) at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent;

(b) a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; and

(c) at least a second anti-cancer agent.

43. In combination, biologically effective amounts of:

(a) at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent;

(b) a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; and

(c) at least a second anti-cancer agent.

44. The kit of claim 20, wherein the targeting agent of said at least a first targeting agent-therapeutic agent construct and the targeting agent of said targeting agent-detectable agent construct are anti-aminophospholipid antibodies, or antigen-binding fragments thereof, obtained from the same antibody preparation or antibody-producing hybridoma.

EXHIBIT B
UNIFIED CLAIMS IN SERIAL NO. 09/351,457 (4001.002300)

2. A method for killing tumor vascular endothelial cells, comprising administering to an animal having a vascularized tumor a biologically effective amount of at least a first binding ligand that comprises a selected cytotoxic agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells.

3. A method for inducing tumor vasculature coagulation, comprising administering to an animal having a vascularized tumor a vessel-occluding amount of at least a first binding ligand that comprises a selected occluding agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of tumor vasculature.

4. A method for destroying tumor vasculature, comprising administering to an animal having a vascularized tumor a tumor-destructive amount of at least a first binding ligand that comprises a selected destructive agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor.

5. A method for treating an animal having a vascularized tumor, comprising administering to said animal a therapeutically effective amount of at least a first binding ligand that comprises at least a first therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor.

6. The method of claim 5, wherein said targeting agent binds to phosphatidylethanolamine on the luminal surface of blood vessels of a vascularized tumor.

7. The method of claim 5, wherein said targeting agent binds to phosphatidylserine on the luminal surface of blood vessels of a vascularized tumor.

8. The method of claim 5, wherein said targeting agent comprises at least a first anti-aminophospholipid antibody or antigen-binding fragment thereof.

9. The method of claim 8, wherein said targeting agent comprises at least a first IgG or IgM anti-aminophospholipid antibody.

10. The method of claim 8, wherein said targeting agent comprises at least a first scFv, Fv, Fab', Fab or $F(ab')_2$ antigen-binding region of an anti-aminophospholipid antibody.

11. The method of claim 8, wherein said targeting agent comprises at least a first human, humanized or part-human chimeric anti-aminophospholipid antibody or antigen-binding fragment thereof.

12. The method of claim 8, wherein said targeting agent comprises at least a first anti-aminophospholipid monoclonal antibody or antigen-binding fragment thereof.

13. The method of claim 12, wherein said targeting agent comprises at least a first anti-aminophospholipid monoclonal antibody, or antigen-binding fragment thereof, that is prepared by a preparative process comprising:

(a) preparing an anti-aminophospholipid antibody-producing cell; and

(b) fusing said anti-aminophospholipid antibody-producing cell with an immortal cell to prepare a hybridoma that produces said anti-aminophospholipid monoclonal antibody.

14. The method of claim 13, wherein said anti-aminophospholipid antibody-producing cell is obtained from a human patient having a disease associated with the production of anti-aminophospholipid antibodies.

15. The method of claim 13, wherein said anti-aminophospholipid antibody-producing cell is obtained by stimulating a mixed population of human peripheral blood lymphocytes with an immunogenically effective amount of an aminophospholipid sample.

16. The method of claim 13, wherein said anti-aminophospholipid antibody-producing cell is obtained by immunizing an animal with an immunogenically effective amount of an aminophospholipid sample.

17. The method of claim 16, wherein the immunized animal is a transgenic mouse that comprises a human antibody library and wherein the anti-aminophospholipid monoclonal antibody is a human monoclonal antibody.

18. The method of claim 13, wherein said preparative process comprises:

(a) obtaining anti-aminophospholipid antibody-encoding nucleic acids from said anti-aminophospholipid antibody-producing cell; and

(b) expressing said nucleic acids to obtain a recombinant anti-aminophospholipid monoclonal antibody.

19. The method of claim 13, wherein said preparative process comprises:

(a) immunizing an animal with an immunogenically effective amount of an aminophospholipid sample;

(b) preparing a combinatorial immunoglobulin phagemid library expressing RNA isolated from the spleen of the immunized animal;

(c) selecting from the phagemid library a clone that expresses an anti-aminophospholipid antibody; and

(d) expressing the anti-aminophospholipid antibody-encoding nucleic acids from said selected clone to provide a recombinant anti-aminophospholipid monoclonal antibody.

20. The method of claim 19, wherein the immunized animal is a transgenic mouse that comprises a human antibody library and wherein the recombinant anti-aminophospholipid monoclonal antibody is a recombinant human monoclonal antibody.

21. The method of claim 5, wherein said targeting agent comprises at least a first aminophospholipid binding protein or an aminophospholipid-binding fragment thereof.

22. The method of claim 21, wherein said targeting agent comprises at least a first annexin or a phosphatidylserine-binding fragment thereof.

23. The method of claim 22, wherein said targeting agent comprises at least a first Annexin V or a phosphatidylserine-binding fragment thereof.

24. The method of claim 21, wherein said targeting agent comprises at least a first phosphatidylethanolamine binding protein or a phosphatidylethanolamine-binding fragment thereof.

25. The method of claim 24, wherein said targeting agent comprises at least a first kininogen or a phosphatidylethanolamine-binding fragment thereof.

26. The method of claim 5, wherein said targeting agent comprises at least two aminophospholipid binding sites.

27. The method of claim 5, wherein said targeting agent is prepared by recombinant expression.

28. The method of claim 5, wherein at least two binding ligands are administered to said animal, wherein said binding ligands each bind to an aminophospholipid and comprise either distinct targeting agents or distinct therapeutic agents.

29. The method of claim 5, wherein said targeting agent is attached to at least a first anticellular or cytotoxic agent that kills or suppresses the growth or cell division of vascular endothelial cells.

30. The method of claim 29, wherein said targeting agent is attached to at least a first steroid, cytokine, antimetabolite, anthracycline, vinca alkaloid, antibiotic, alkylating agent, epipodophyllotoxin, DNA synthesis inhibitor, daunorubicin, doxorubicin or adriamycin.

31. The method of claim 29, wherein said targeting agent is attached to at least a first plant-, fungus- or bacteria-derived toxin.

32. The method of claim 31, wherein said targeting agent is attached to at least a first A chain toxin, bacterial endotoxin, lipid A moiety of bacterial endotoxin, ribosome inactivating protein, α-sarcin, gelonin, aspergillin, restrictocin, ribonuclease, diphtheria toxin or *Pseudomonas* exotoxin.

33. The method of claim 32, wherein said targeting agent is attached to at least a first ricin A chain or deglycosylated ricin A chain.

34. The method of claim 5, wherein said targeting agent is attached to at least a first coagulation factor.

35. The method of claim 34, wherein said targeting agent is attached to at least a first human coagulation factor.

36. The method of claim 34, wherein said targeting agent is attached to at least a first coagulation factor selected from the group consisting of Factor II/IIa, Factor VII/VIIa, Factor IX/IXa, Factor X/Xa, a vitamin K-dependent coagulation factor that lacks the Gla modification, Russell's viper venom Factor X activator, thromboxane A_2, thromboxane A_2 synthase and α2-antiplasmin.

37. The method of claim 34, wherein said targeting agent is attached to at least a first Tissue Factor, dimeric Tissue Factor, trimeric Tissue Factor, polymeric Tissue Factor, mutant Tissue Factor or Tissue Factor derivative.

38. The method of claim 37, wherein said targeting agent is attached to at least a first truncated Tissue Factor.

39. The method of claim 5, wherein said targeting agent is attached to at least two distinct therapeutic agents.

40. The method of claim 5, wherein said at least a first therapeutic agent is directly attached to said targeting agent by a direct covalent bond, via a chemical cross-linker or by recombinant expression as a fusion protein.

41. The method of claim 5, wherein said at least a first therapeutic agent is attached to said targeting agent via an antibody, or antigen binding region thereof, that binds to said therapeutic agent.

42. The method of claim 41, wherein said binding ligand is a bispecific antibody that comprises a first, targeting antibody, or antigen binding fragment thereof, that binds to an aminophospholipid; operatively attached to a second antibody, or antigen binding fragment thereof, that binds to said at least a first therapeutic agent.

43. The method of claim 5, wherein said binding ligand comprises an anti-phosphatidylserine antibody, or antigen binding fragment thereof, that is directly or indirectly attached to truncated Tissue Factor.

57. The method of claim 5, wherein said animal is a human patient.

58. A method for treating cancer, comprising administering to an animal having a vascularized tumor at least a first pharmaceutical composition comprising an amount of at least a first binding ligand effective to kill at least a portion of the intratumoral vascular endothelial cells; wherein said binding ligand comprises at least a first cytotoxic agent operatively attached to a targeting agent that binds to an aminophospholipid expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

59. A method for treating cancer, comprising administering to an animal having a vascularized tumor at least a first pharmaceutical composition comprising an amount of at least a first binding ligand effective to occlude or destroy intratumoral vasculature, the binding ligand comprising at least a first coagulative or destructive agent operatively attached to a targeting agent that binds to an aminophospholipid expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

60. A method for treating cancer, comprising administering to an animal with a vascularized tumor at least a first pharmaceutical composition comprising an amount of at least a first binding ligand effective to induce tumor necrosis, the binding ligand comprising at least a first therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid expressed on the luminal surface of intratumoral blood vessels of the vascularized tumor.

61. A method for treating an animal having a vascularized tumor, comprising administering to said animal a therapeutically effective amount of a pharmaceutical composition comprising at least a first construct comprising an anti-aminophospholipid antibody, or antigen binding fragment thereof, directly or indirectly linked to at least a first therapeutic agent.

62. The method of claim 61, wherein said construct comprises an anti-phosphatidylserine antibody, or antigen binding fragment thereof, that is directly or indirectly attached to truncated Tissue Factor.

66. A method for delivering a selected therapeutic agent to tumor vasculature, comprising administering to an animal having a vascularized tumor a biologically effective amount of at least a first binding ligand that comprises said selected therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor.